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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,243	08/30/2001	Rolland F. Hebert		9377

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EXAMINER

YOUNG, JOSEPHINE 4

ART UNIT	PAPER NUMBER
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1623

DATE MAILED: 03/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

<p align="center">Office Action Summary</p>	<p>Application No.</p> <p align="center">09/943,243</p>	<p>Applicant(s)</p> <p align="center">HEBERT, ROLLAND F.</p>	
	<p>Examiner</p> <p align="center">Josephine Young</p>	<p>Art Unit</p> <p align="center">1623</p>	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 is/are pending in the application.
- 4a) Of the above claim(s) 8-13 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-7 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☒ Claim(s) 1-13 are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413) Paper No(s). <u>3</u> . |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>2</u> . | 6) <input type="checkbox"/> Other: |

DETAILED ACTION***Information Disclosure Statement***

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-7, drawn to pharmaceutical compositions comprising (a) a pharmaceutically acceptable carrier and (b) an optically pure enantiomer (S,S)-S-adenosylmethionine or a non-racemic mixture of (S,S)-S-adenosylmethionine and (R,S)-S-adenosylmethionine, and/or (c) one or more pharmaceutically acceptable salt, classified in class 514, subclass 46.
- II. Claims 8-13, drawn to methods for using such compositions, classified in class 514, subclass 46.

The inventions are distinct, each from the other because of the following reasons:

Art Unit: 1623

Groups I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the processes as claimed can be practiced with another materially different product, namely compositions comprising a racemic mixture of S-adenosylmethionine and/or a racemic mixture of pharmaceutically acceptable salt of S-adenosylmethionine.

Because these inventions are distinct for the reason given above and have acquired a separate status in the art as shown by their recognized divergent subject matter, restriction for examination purposes as indicated is proper. A reference for one group could not reasonably be expected to be a reference for the other. Further, searching both of the inventions constitutes a burdensome search, as a thorough search comprises a search of foreign patents and non-patent literature, as well as the appropriate U.S. patent classifications. To search the two independent and distinct inventions, set forth supra, would indeed impose an undue burden upon the examiner in charge of this application.

During a telephone conversation with Applicant, Rolland F. Hebert, on March 11, 2003, a provisional election was made without traverse to prosecute the invention of Group I, claims 1-7. Affirmation of this election must be made by applicant in replying to this Office action.

Claims 8-13 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification

The disclosure is objected to because of the following informalities: Example 1 is ambiguous. In particular, it is unclear as to whether (S,S)-S-adenosylmethionine is administered to the volunteers or if a stabilized p-toluene sulfonate salt of (S,S)-S-adenosylmethionine (as per US Patent No. 4,028,183 to FIECCHI) is administered.

Further, the disclosure is objected to because of the following informalities: The specification does not consistently refer to S-adenosylmethionine with the same nomenclature.

Appropriate correction is required.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The claims are directed to pharmaceutical compositions comprising: (a) a pharmaceutically acceptable carrier and (b) an optically pure enantiomer (S,S)-S-adenosylmethionine or a non-racemic mixture of (S,S)-S-adenosylmethionine and (R,S)-S-adenosylmethionine, and/or (c) one or more pharmaceutically acceptable salt. However, the specification does not describe such compositions. Further, claims 2-3 are directed to particular ratios for the non-racemic mixture; however, these limitations are not specifically disclosed in the specification. Finally, claims 4-7 are directed to particular salts of S-adenosylmethionine. While it is clear that the specification is directed to salts of enantiomerically pure or enriched S-adenosylmethionine, no particular salt is explicitly indicated other than the p-toluene sulfonate salt of (S,S)-S-adenosylmethionine in Example 1 on page 14. Therefore, it is suggested that

Art Unit: 1623

Applicant amend the specification to include the claim limitations, such as the particular compositions, ratios and salts, to overcome the present objection.

Claim Objections

Claim 4 is objected to because of the following informalities: The formulas are not represented in an acceptable format. Superscripting and subscripting should not be informally indicated but rather should be set forth as such.

Claim 4 also is objected to because of the following informalities: The claim indicates that the salt for each enantiomer is selected from a group; however the salts are not described in a grammatically consistent manner. For example, one species of the group is recited as “a lipophilic salt of S-adenosyl-L-methionine is a member selected from ...”; however, another species of the group is recited as “S-adenosyl-L-methionine or a pharmaceutically acceptable salt thereof and an effective amount of a lithium salt selected from the group consisting of ...”, while another member of the group is recited as a “water-soluble salt of a bivalent or trivalent metal is a member selected from the group consisting of ...”.

Further, claims 4 and 6 are objected to because of the following informalities: The claims do not consistently refer to S-adenosylmethionine with the same nomenclature. It is noted that in claim 4, S-adenosylmethionine is parenthetically defined as SAM; however, further in the claim, it is referenced as S-adenosyl-L-methionine and SAM-e. Claim 6 references S-adenosyl-L-methionine.

Claim 5 is objected to because of the following informalities: The claim recites chloride twice.

Art Unit: 1623

Finally, Claim 4 is objected to because of the following informalities: Claim 4 does not end in a period.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected as failing to define the invention in the manner required by 35 U.S.C. 112, second paragraph.

The term "substantially" in claim 1 is a relative term that renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear as to what degree of enantiomeric enrichment is necessary to be construed as substantially optically pure.

The phrase "their pharmaceutically acceptable salts" in claim 1 renders the claim indefinite because it is unclear as to if the salts are an additional component of the composition or an alternative component of the composition.

The phrase "in particular" in claim 4 renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Art Unit: 1623

The phrase "double and single salts of S-adenosyl-L-methionine with sulphuric acid and p-toluenesulphonic acid" in claim 6 renders the claim indefinite because it is unclear how a single salt can be from sulphuric acid and p-toluenesulphonic acid.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by the article DUNNE et al., British Journal of Pharmacology, **1998**, *125*, 225-233 (U).

Applicant claims pharmaceutical compositions comprising enantiomerically pure or enriched S-adenosyl-L-methionine, or salts thereof. Further, Applicant claims compositions wherein the ratio of (S,S)-S-adenosyl-L-methionine : (R,S)-S-adenosyl-L-methionine is 80-100 : 20-0, or 95-100 : 5-0. Applicant also claims compositions comprising particular salts and double salts of S-adenosyl-L-methionine.

DUNNE teaches that the choleretic activity of (S,S)-S-adenosyl-L-methionine is disproportionately greater. See abstract. Further, DUNNE teaches on page 230, right column, lines 4-9, that the two diastereomers of S-adenosyl-L-methionine (SAM), endogenous S,S and pharmaceutically derived R,S, show distinct characteristics in improving blood flow and bile production, with equimolar amounts of the former more choleretic and of the latter more active haemodynamically. On page 226, left column, Methods section, under the Drugs heading,

Art Unit: 1623

DUNNE teaches that the (S,S) and (R,S) diastereomers of S-adenosyl-L-methionine (SAM) used were 1,4-butanedisulphonate salts. Finally, on page 226, right column, first full paragraph, DUNNE teaches that the salts of the (S,S) and (R,S) diastereomers of S-adenosyl-L-methionine (SAM) were administered in oxygenated bicarbonate-buffered saline.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over the article DUNNE (U) in view of the article MATOS et al., Bioorganic Chemistry, 1987, 15, 71-80 (V).

Applicant claims pharmaceutical compositions comprising salts of enantiomerically pure or enriched S-adenosyl-L-methionine, or salts thereof. Applicant also claims particular single and double salts of S-adenosyl-L-methionine with sulphuric acid and p-toluenesulphonic acid.

Art Unit: 1623

As set forth supra, DUNNE teaches that the choleretic activity of (S,S)-S-adenosyl-L-methionine is disproportionately greater. See abstract. Further, DUNNE teaches on page 230, right column, lines 4-9, that the two diastereomers of S-adenosyl-L-methionine (SAM), endogenous S,S and pharmaceutically derived R,S, show distinct characteristics in improving blood flow and bile production, with equimolar amounts of the former more choleretic and of the latter more active haemodynamically. On page 226, left column, Methods section, under the Drugs heading, DUNNE teaches that the (S,S) and (R,S) diastereomers of S-adenosyl-L-methionine (SAM) used were 1,4-butanedisulphonate salts. Finally, on page 226, right column, first full paragraph, DUNNE teaches that the salts of the (S,S) and (R,S) diastereomers of S-adenosyl-L-methionine (SAM) were administered in oxygenated bicarbonate-buffered saline.

DUNNE does not explicitly state that other salts, such as single and double salts of the (S,S) and (R,S) diastereomers of S-adenosyl-L-methionine (SAM) with sulphuric acid and p-toluenesulphonic acid can be used.

MATOS teaches that sulfonium counterions affect the stability of S-adenosyl-L-methionine to epimerization. See abstract. Further MATOS teaches on pages 74-76, that the rate of epimerization decreases with an increase in the concentration of tosylate, and tosylate and sulfate stabilize to epimerization the best. See in particular Figure 4, on page 76.

It would have been obvious to one of ordinary skill in the art to use the any tosylate or sulfate salt to stabilize the (S,S) and (R,S) diastereomers of S-adenosyl-L-methionine (SAM). A skilled artisan would have been motivated and have had a reasonable expectation of success to make and use such salts, as such salts are common in the pharmaceutical art and MATOS

Art Unit: 1623

teaches that such salts stabilize the diastereomers of S-adenosyl-L-methionine (SAM) to epimerization.

Conclusion

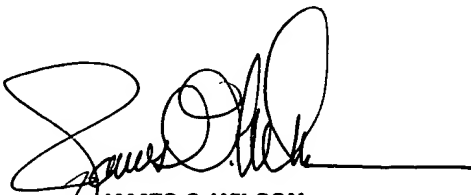
Claims 1-13 are pending. Claims 1-7 are rejected. Claims 8-13 are withdrawn. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Josephine Young whose telephone number is (703) 605-1201. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached at (703) 308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

JY
March 14, 2003


JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600